

## **REMARKS**

Claims 1-9, 11-17, and 52-66 are pending in this application. Claims 1-9 and 11-17 are presently withdrawn because they are not within the scope of applicants' provisional election. Claims 52-66 are amended herein. Claim 1 is also amended to preserve unity of invention between claims 1 and 52.

Claims 52-66 are rejected. Applicants respectfully request reconsideration of the rejection of claims 52-66 for the reasons set forth below.

### Applicants continued traverse of restriction requirement

Applicants maintain it is improper to require restriction between claims 1-9 and 11-17 from claims 52-66. Restriction practice in this U.S. national phase application is governed by PCT Rule 13, 37 CFR § 1.475, and MPEP 1893.03(d). There is unity of invention between claims 1 and 52 because these claims share the common technical feature that cell aggregates are embedded according to a predetermined, non-random pattern, wherein the cell aggregates have predetermined positions in the pattern. None of the references cited in the Office action show this common technical feature. Applicants reserve the right to challenge the propriety of this restriction requirement by petition under 37 CFR 1.144. Applicants note 37 CFR 1.144 allows this petition to be deferred until after final action on or allowance of the elected claims. Applicants are deferring this petition with the hope this response can avoid the need for a petition.

### Response to claim objections

Claims 53-63 and 66 are amended herein to include commas before the word "wherein" in response to the objection to these claims. Although there is no proper legal basis for objecting to claims based on a stylistic decision whether or not to use commas before the word "wherein" in dependent claims, the commas do not change the meaning of the claims and this issue is now moot because of the amendments to the claims.

### Response to prior art rejections

Applicants believe the amended claims are patentable over the cited art for at least the following reasons.

### *1. Background*

As is explained in the specification of the present application, when cell aggregates are embedded in a biocompatible matrix, the structural evolution of the physical structure formed by the cells depends on a number of variables including adhesive forces between the cells, adhesive and cohesive forces between the cells and the matrix, the characteristics of the matrix (including composition and spatial structure), and the pattern by which the cell aggregates are embedded in the matrix. See paragraph [0082] of the present application as published (US 20080070304). The specification of the present application further explains that interaction of these variables can affect whether the cell aggregates evolve into a desired structure (e.g., a hollow tubular structure or other desired structure) or fail to evolve into the desired structure (e.g., by breaking up into multiple undesired structures). Depending on the properties of the matrix, the characteristics of the cell aggregates, and the embedding pattern, the structure might or might not evolve into a desired structure. In some cases, the cells from the aggregates may disperse into the matrix and thereby prevent the desired structure from being attained. In other cases the cells may collapse into an undesired structure, such as one or more spherical structures. See paragraph [0089] of application as published.

The applicants have developed technology that enables desirable results to be obtained on a reliable basis. As explained in paragraphs [0081]-[0095], one or more of the variables affecting structural evolution of plurality of cell aggregates embedded in a matrix, such as the embedding pattern, can be controlled/selected to ensure the structure evolves into a desired structure. The skilled person recognizes from the specification that the structural evolution is governed by the small scale cell-to-cell adhesion and cell-to-cell or cell-to-matrix cohesion forces. Further, the skilled person understands that changes in the embedding pattern that could affect whether and how the cells constituting one cell aggregate interact with the cells constituting other cell aggregates in the pattern can be relevant to the ability to achieve a desired result. The skilled person also understands the phrase "predetermined pattern" in the present application refers to a pattern in which the particular positions of individual cell aggregates are known and planned beforehand to limit variability in the way cells from different cell aggregates interact with one another as the structure evolves and the cell aggregates merge to form a desired engineered tissue. The independent claims have been amended to more particularly recite the cell aggregates have "predetermined positions in the pattern" to more particularly highlight this difference between the invention and the prior art.

The Office action includes a statement that the Examiner is a person of ordinary skill in the art because examiners "have general and specific knowledge of the technical subject matter

and the pertinent scientific and technical literature presented in front of them." Applicants note for the record that examining patent applications in a particular field does not necessarily equate to possessing ordinary skill of a person working in that field. This is implicit in the admonition from *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ.2d 1464, 1468 (Fed. Cir. 1999) and MPEP 2111.01 that the broadest interpretation of claims used by the Office during examination must be consistent with the interpretation that those skilled in the art would reach. This admonition would be meaningless if examiners are considered to have ordinary skill in the art just because of the knowledge obtained by examining patent applications. The admonition is necessary to remind examiners of the bounds on the mandate to interpret claims broadly during prosecution and guard against overly zealous application of the mandate to interpret claims broadly.

In this case, interpretations of "predetermined pattern" that include a large macro pattern (e.g., a circle formed by spraying or ink jetting a solution containing cell aggregates onto a gel) or a pattern formed by packing a plurality of irregularly shaped aggregates right next to each other so they are likely to merge are inconsistent with the interpretation of "predetermined pattern" those skilled in the art would reach. In particular, the skilled person would conclude these patterns are not predetermined because the particular positions of the cell aggregates in the pattern are not determined beforehand. This can introduce undesirable variations in the way the cell-to-cell and cell-to-matrix forces of adhesion and cohesion that govern structural evolution impact the structure produced by the cell aggregates after maturation.

## *2. Claims 52-53, 56, 58, and 62-63 are not anticipated by Furukawa*

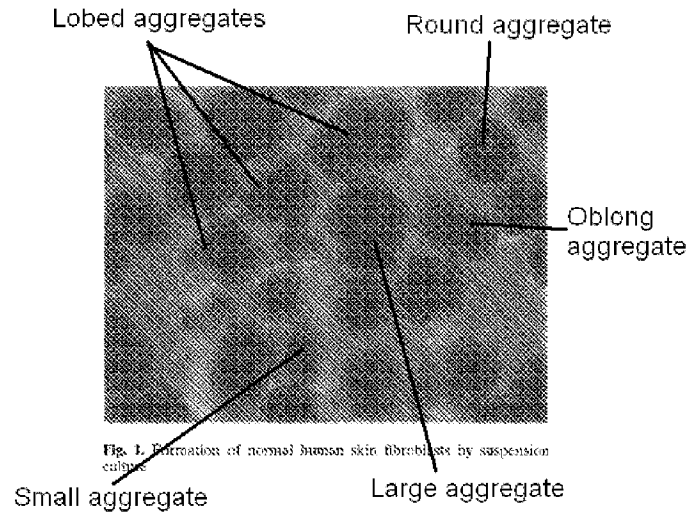
Claim 52 is directed to "[a] three-dimensional layered structure comprising: at least one layer of a matrix; and a plurality of cell aggregates, each cell aggregate comprising a plurality of living cells; **wherein the cell aggregates are embedded in the at least one layer of matrix in a non-random predetermined pattern, the cell aggregates having predetermined positions in the pattern.**" (Emphasis added.)

Claim 52 is unanticipated by Furukawa (J. Artif. Organs 2001 4: 353-356) for at least the reason that Furukawa fails to disclose any structure including a plurality of cell aggregates embedded in a matrix according to a non-random predetermined pattern in which the cell aggregates have predetermined positions within the pattern. Support for the amendment is found in at least paragraphs [0041], [0081]-[0098], [0101], [0118], and [0121] of the published application as well as Figs. 8A-8L, 11A, 12, 13, and 16A-18.

Furukawa discloses a method of making tissue-engineered skin by inoculating a three dimensional scaffold with fibroblast aggregates. Contrary to the assertions in the Office action, the fibroblasts are not embedded in the scaffold according to a predetermined, non-random pattern. Furukawa also fails to disclose the cell aggregates have predetermined positions within the pattern. After forming the cells into aggregates, Furukawa inoculates the aggregates into a scaffold by adding 1.5 to 2.0 ml of a fluid medium containing aggregates to a dish containing the scaffold. There is no control over where any individual cell aggregates are positioned. The dish containing the scaffold and aggregates is placed on a shaker and the shaking action results in the aggregates becoming trapped in and attached to the scaffold mesh. There is no attempt to control where any particular cell aggregates are positioned when they become trapped in or attached to the scaffold. On the contrary, the incorporation of the cell aggregates into the scaffold in Furukawa is randomized by the method of inoculation with a fluid medium containing suspended aggregates followed by shaking to get aggregates trapped in the scaffold. In particular, there is no control or planning of where the individual cell aggregates are positioned when they become trapped in or attached to the scaffold. Instead, the pattern formed by the aggregates after they are trapped in the scaffold is the result of chaotic processes such as shaking that cause the aggregates to move relative to the scaffold in unpredictable ways before they eventually become trapped in and attached to the scaffold.

Accordingly, claim 52 is unanticipated by Furukawa for at least the reason that Furukawa fails to disclose a structure in which cell aggregates are embedded in the at least one layer of a matrix in a non-random predetermined pattern in which the positions of the cell aggregates in the pattern are predetermined. Claims 53, 56, 58, and 62-63 depend from claim 52 and are unanticipated for at least the same reasons.

Claim 53 further specifies the cell aggregates are substantially uniform in size and shape. Furukawa fails to disclose this. Furukawa does disclose aggregates that are smoothed by incubation for 24-36 hours in a rotational culture. However, Fig. 1 of Furukawa illustrates that there are cell aggregates are not substantially uniform in size and shape.



The annotated version of Fig. 1 of Furukawa reproduced above illustrates there are significant differences in the size and shape of the aggregates disclosed by Furukawa. It would be difficult to control the precise location where Furukawa's irregularly sized and shaped cell aggregates are embedded. It would also be difficult to assess the impact the irregularities in size and shape of the aggregates might impact structural evolution of the structure formed by embedding these cell aggregates in a matrix. Thus, claim 53 is unanticipated for at least the additional reason Furukawa fails to disclose structure as recited in claim 52 wherein the cell aggregates are substantially uniform in size and shape.

Claim 56 further specifies that the cell aggregates are substantially spherical. The specification explains the phrase "substantially spherical" means the principle radii of curvature of the cell aggregate are substantially equal at all points on the surface of the aggregate (i.e., vary by about 10% or less over all points on the surface of the aggregate). See paragraph [0039] of application as published. The lobed aggregates and oblong aggregate referenced in the annotated of Fig. 1 from Furukawa above are clearly not substantially spherical because there are wide variations in the radius of curvature depending on whether the surface point is at the end of a lobe, at a crease between two lobes, or at a broader flatter surface (e.g., along the broader side of an oblong aggregate). Although some of the aggregates appear round in Fig. 1, it cannot be assumed the aggregates appearing round are spherical because Fig. 1 only shows the shape of the aggregates in a single cross section. In view of the irregularities in the size and shape that are apparent in the population of aggregates, it appears irregularities in the shape of the aggregates in Furukawa are common and it is not inherent that any aggregates in Furukawa are substantially spherical. Thus, claim 56 is unanticipated for at least this additional reason.

3. *Claims 52-53 and 56-66 are not obvious over Furukawa in view of Boland (US 20040237822) and Roth (Biomaterials, Vol. 25, pp. 3707-3715 (2004))*

The Roth article is not prior art because this application claims priority to the provisional application filed February 24, 2004 and the Roth article was published at Volume 25, Issue 17 of Biomaterials in August of 2004. Moreover, the Office action does not cite to any particular disclosure in Roth to support the rejection and instead discusses only Furukawa and Boland. Thus, it appears citation to Roth in the rejection may be a mistake. The Examiner is invited to telephone the undersigned if this is not the case.

As previously noted, Furukawa fails to disclose a structure including cell aggregates embedded in a matrix in a non-random predetermined pattern in which the cell aggregates have predetermined positions within the pattern. The addition of the Boland reference does nothing to cure the failure of Furukawa to disclose or suggest a plurality of cell aggregates embedded in a matrix according to a predetermined pattern in which the positions of the cell aggregates in the pattern are predetermined. Thus, claim 52 is not rendered obvious by the combination of Furukawa for at least these reasons. Claims 53 and 56-66 depend from claim 52 and are patentable for at least the same reasons.

4. *Claims 54-55 are not obvious over Furukawa in view of Boland (US 20040237822), Roth (Biomaterials, Vol. 25, pp. 3707-3715 (2004)), and Mizumoto (Cytotechnology, Vol. 31 pp. 69-75)*

Claims 54-55 depend from claim 52 and are patentable for at least the same reasons. The addition of the Mizumoto reference does nothing to cure the failure of Furukawa and Boland to disclose or suggest a plurality of cell aggregates embedded in a matrix according to a predetermined pattern in which the positions of the cell aggregates in the pattern are predetermined. Thus, claims 54 and 55 are non obvious for at least the same reasons discussed above in connection with claim 52.

**CONCLUSION**

The Commissioner is hereby authorized to charge any fees that are required for this response and not otherwise provided to Deposit Account No. 19-1345.

Respectfully submitted,

A handwritten signature in black ink that reads "N. Chris Walters". The signature is written in a cursive, flowing style.

N. Chris Walters, Reg. No. 52,338  
SENNIGER POWERS LLP  
100 North Broadway, 17th Floor  
St. Louis, Missouri 63102  
(314) 231-5400

KFJ/NCW/bcw